IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Yokoyama et al.
App. No	:	10/589,420
Filed	:	August 15, 2006
For	:	Anti NC1 monoclonal antibody
Examiner	:	Grun, James Leslie
Art Unit	:	1641
Conf No.	:	9866

DECLARATION UNDER 37 CFR § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, _Tsukao Yokoyama_, a co-inventor of the above-captioned application, declare and state as follows:

1. I am a co-inventor of the subject matter claimed in the above-captioned application. I received my Bachelar degree in Pharmacology from Toyama University. Currently, I am a pharmacologist and CEO in Collagen Research Center of the . I have been at this position and related positions since 1981.

2. The currently pending Claims 21, 26-33 and 35-37 recite a method of identifying presence of nephritis in a mammal at an early stage before formation of glomerular crescent or deposition of Immunoglobulin. With respect to such a detection at an early stage, the Examiner asserted that, in the absence of any showing of the timing of the appearance of significant levels of the epitope detected by the NC1 monoclonal antibody, it would seem unknown and unpredictable that the antigen would be detectable at detectably different levels in mammals with early stage disease and not only after disease has manifested in the hosts.

3. I present the following comments in order to explain that the presently claimed method can be used to detect the nephritis condition in an early stage.

4. Nearly all forms of acute glomerulonephritis have a tendency to progress to chronic glomerulonephritis. If the disease progression is not treated with proper therapy, it results in chronic kidney disease (CKD) and other conditions. The U.S. National Kidney Foundation defines CKD as (1) evidence of kidney damage based on abnormal urinalysis results (e.g., proteinuria, hematuria) or structural abnormalities observed on ultrasound images or (2) a glomerular filtration rate (GFR) of less than 60 mL/min for 3 or more months. Based on this definition, the National Kidney Foundation developed guidelines that classify the progression of renal disease into 5 stages, from kidney disease with a preserved GFR to end-stage kidney failure, as follows:

Stage 1: This stage is characterized by kidney damage with a normal GFR ($\geq$ 90 mL/min).

Stage 2: This stage is characterized by kidney damage with a mild decrease in the GFR (60-90 mL/min).

Stage 3: This stage is characterized by a moderately decreased GFR (30-59 mL/min).

Stage 4: This stage is characterized by a severe decrease in the GFR (15-29 mL/min).

Stage 5: This stage is characterized by kidney failure.

As evidence supporting the foregoing information, the accompanying Exhibit A is submitted herewith.

5. Among the above five stages of CKD, Stages 1-3 are generally considered as the early stages of renal disease. While the GFR value is an important index for determining the stage of the renal disease, this value is generally maintained largely close to the normal level during Stages 1 and 2. Thus, measurement of GFR values would not be very helpful to diagnose the disease condition and/or progression at the early stages.

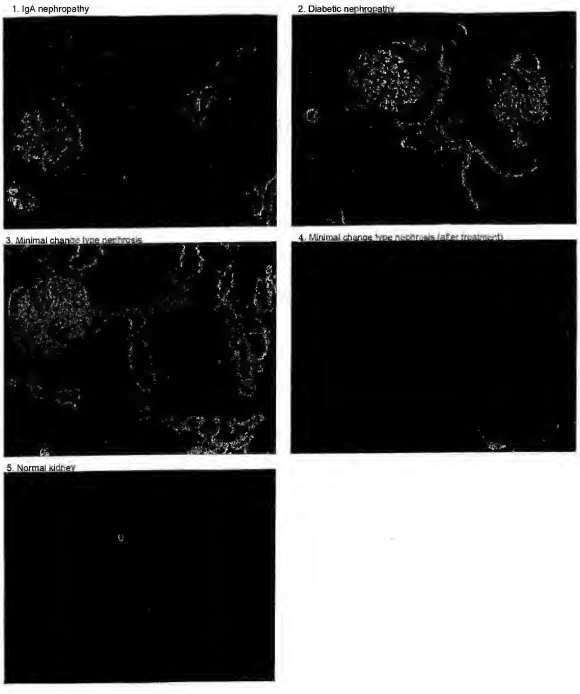
6. In addition to the GFR value, the level of serum creatinine is used as another index to determine the stage of the renal disease. However, a rise in serum creatinine levels,

which is an indication of the progression of the disease, is apparent when the GFR decreases less than 60-70 mL/min. Furthermore, when the serum creatinine levels are notably changed, it is typically after more than 50% of kidney function is lost. Accordingly, measurement of the serum creatinine levels would not be helpful to diagnose the disease during the early stages.

7. As mentioned above, measurement of two well-known indexes, which are GFR values and serum creatinine levels, would not be reliable means to determine the nephritis condition during the early stages. In addition, there are generally no pathological signs such as deposition of Ig and glomerular crescent, which indicate the disease progression, at Stages 1 and 2. Therefore it is very difficult to diagnose the disease early.

8. Early detection of the renal disease is crucial to provide proper treatment to a patient. At Stages 1 and 2, slowing down the disease progression and mild treatment would be sufficient to treat the disease; however, if a patient reaches Stage 4 or 5, the replacement of kidney may be necessary. Therefore, any means to identify the renal disease at early stages is of great importance. (*See* Exhibit A for more details regarding treatment plans for each stage)

8. The co-inventor and I have invented a method that can identify presence of nephritis in a mammal by using a specific monoclonal anti-NC1 antibody. We generated and selected this antibody that has a highly specific binding affinity to a sample with nephritis but not to a normal sample. Further, we discovered that our method can detect the renal disease condition even prior to glomerular crescent formation and Ig deposition. Therefore, this method can be applicable to detect the disease condition at the early stages when no pathological signs are observed. We presented the data showing the efficacy of this method in Figure 4 of the present application. In this test demonstrated in the figure, we applied the method to various human kidney tissue samples including a sample obtained from a patient with minimal change type of nephritis. The minimal change type of nephritis is hard to detect because Ig deposition and/or renal crescent is rarely observed and the patient's renal tissue generally appears normal and healthy. The data are provided in Figure 4 are reproduced below for convenience.



As readily seen in the above figure, only panels 1-3 show positive signals. Panels 1 and 2 are positive controls and panel 3 represents a sample with the minimal change type nephrosis condition. The signal intensity from panel 3 is highly comparable to those from panels 1 and 2. When we applied the method to another sample with the minimal change type nephrosis which

was treated already, the signal disappeared as seen in panel 4. These data clearly prove that our tested method can detect the presence of the renal disease condition before any pathological signs (e.g. Ig deposition/renal crescent formation) are developed.

9. In view of the foregoing comments and data, it is clear that the method according to the present application can detect the renal disease condition at the early stage of the disease when no substantial sign of the disease is apparent.

10. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements and the like so made are punishable by fine or imprisonment, or both, under Section 101 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: 01/10/2011 Signed: Tsukao Yokoyama

Printed Name Tsukao Yokoyama

10277528
011011

Exhibit A

Glomerulonephritis, Chronic

Author: Moro O Salifu, MD, MPH, FACP, Associate Professor, Department of Internal Medicine, Chief, Division of Nephrology, Director of Nephrology Fellowship Program and Transplant Nephrology, State University of New York Downstate Medical Center
Coauthor(s): Barbara G Delano, MD, MPH, Director of Home Hemodialysis and Peritoneal Dialysis, Professor, Department of Internal Medicine, Division of Nephrology, State University of New York at Brooklyn
Contributor Information and Disclosures

Updated: Oct 23, 2009

Introduction

Background

Nearly all forms of acute glomerulonephritis have a tendency to progress to chronic glomerulonephritis. The condition is characterized by irreversible and progressive glomerular and tubulointerstitial fibrosis, ultimately leading to a reduction in the glomerular filtration rate (GFR) and retention of uremic toxins. If disease progression is not halted with therapy, the net result is chronic kidney disease (CKD), end-stage renal disease (ESRD), and cardiovascular disease. The diagnosis of CKD can be made without knowledge of the specific cause.

The National Kidney Foundation defines CKD as (1) evidence of kidney damage based on abnormal urinalysis results (eg, proteinuria, hematuria) or structural abnormalities observed on ultrasound images or (2) a GFR of less than 60 mL/min for 3 or more months. Based on this definition, the National Kidney Foundation developed guidelines that classify the progression of renal disease into 5 stages, from kidney disease with a preserved GFR to end-stage kidney failure. This classification includes treatment strategies for each progressive level, as follows:

- Stage 1: This stage is characterized by kidney damage with a normal GFR (≥ 90 mL/min). The action plan is diagnosis and treatment, treatment of comorbid conditions, slowing of the progressing of kidney disease, and reduction of cardiovascular disease risks.
- Stage 2: This stage is characterized by kidney damage with a mild decrease in the GFR (60-90 mL/min). The action plan is estimation of the progression of kidney disease.

- Stage 3: This stage is characterized by a moderately decreased GFR (30-59 mL/min). The action plan is evaluation and treatment of complications.
- Stage 4: This stage is characterized by a severe decrease in the GFR (15-29 mL/min). The action plan is preparation for renal replacement therapy.
- Stage 5: This stage is characterized by kidney failure. The action plan is kidney replacement if the patient is uremic.

At the later stages of glomerular injury, biopsy results cannot help distinguish the primary disease. Histology and clues to the etiology are often derived from other systemic diseases, if present. Considerable cause-specific variability is observed in the rate at which acute glomerulonephritis progresses to chronic glomerulonephritis.

Pathophysiology

Reduction in nephron mass from the initial injury reduces the GFR. This reduction leads to hypertrophy and hyperfiltration of the remaining nephrons and to the initiation of intraglomerular hypertension. These changes occur in order to increase the GFR of the remaining nephrons, thus minimizing the functional consequences of nephron loss. The changes, however, are ultimately detrimental because they lead to glomerulosclerosis and further nephron loss.

In early renal disease (stages 1-3), a substantial decline in the GFR may lead to only slight increases in serum creatinine levels. Azotemia (ie, a rise in BUN and serum creatinine levels) is apparent when the GFR decreases to less than 60-70 mL/min. In addition to a rise in BUN and creatinine levels, the substantial reduction in the GFR results in decreased production of (1) erythropoietin, thus resulting in anemia; (2) decreased production of vitamin D, resulting in hypocalcemia, secondary hyperparathyroidism, hyperphosphatemia, and renal osteodystrophy; (3) reduction in acid, potassium, salt, and water excretion, resulting in acidosis, hyperkalemia, hypertension, and edema; and (4) platelet dysfunction, leading to increased bleeding tendencies.

Accumulation of toxic waste products (uremic toxins) affects virtually all organ systems. Azotemia occurring with the signs and symptoms listed above is known as uremia. Uremia occurs at a GFR of approximately 10 mL/min. Some of these toxins (eg, BUN, creatinine, phenols, guanidines) have been identified, but none has been found to be responsible for all the symptoms.

Frequency

United States

Chronic glomerulonephritis is the third leading cause of ESRD and accounts for 10% of patients on dialysis in the United States.

International

Chronic glomerulonephritis accounted for up to 40% of patients on dialysis in Japan and some Asian countries. However, more recent data suggest that, in Japan for instance, the rate of chronic glomerulonephritis in patients on dialysis is 28%. The cause of this declining rate is not known. Concurrent with the decline in chronic glomerulonephritis in these countries is an increase in diabetic nephropathy in up to 40% of patients on dialysis.

Mortality/Morbidity

ESRD and death are common outcomes unless renal replacement therapy is instituted.

Clinical

History

The history should focus on cause-specific symptoms to determine the causes of CKD (if unknown) and on symptoms related to uremia to determine if renal replacement therapy is needed.

- Cause-specific history: Obtain a cause-specific history so that further workup and management of the disease (if systemic) can be planned.
- Uremia-specific history
  - The following symptoms suggest uremia:
    - Weakness and fatigue
    - Loss of energy, appetite, and weight
    - Pruritus
    - Early morning nausea and vomiting
    - Change in taste sensation
    - Reversal in sleep pattern (ie, sleepiness in daytime, wakefulness at night)
    - Peripheral neuropathy
    - Seizures
    - Tremors
  - The presence of edema and hypertension suggests volume retention.
  - Dyspnea or chest pain that varies with position suggests fluid overload and pericarditis, respectively.
  - Leg cramps may suggest hypocalcemia or other electrolyte abnormalities.
  - Weakness, lethargy, and fatigue may be due to anemia.

Physical

Cause-specific physical examination findings are discussed in articles on the specific causes. See Causes for links to such articles.

- Uremia-specific findings
  - Hypertension
  - Jugular venous distension (if severe volume overload is present)
  - Pulmonary rales (if pulmonary edema is present)
  - Pericardial friction rub in pericarditis
  - Tenderness in the epigastric region or blood in the stool (possible indicators for uremic gastritis or enteropathy)
  - Decreased sensation and asterixis (indicators for advanced uremia)

Causes

The progression from acute glomerulonephritis to chronic glomerulonephritis is variable. Whereas complete recovery of renal function is the rule for patients with poststreptococcal glomerulonephritis, several other glomerulonephritides, such as immunoglobulin A (IgA) nephropathy, often have a relatively benign course and many do not progress to ESRD.

- Rapidly progressive glomerulonephritis or crescentic glomerulonephritis: Approximately 90% of patients progress to ESRD within weeks or months.

- Focal segmental glomerulosclerosis: Approximately 80% of patients progress to ESRD in 10 years. Patients with the collapsing variant, which is termed malignant focal segmental glomerulosclerosis, have a more rapid progression. This form may be idiopathic or related to HIV infection.
- Membranous nephropathy: Approximately 20-30% of patients with membranous nephropathy progress to chronic renal failure (CRF) and ESRD in 10 years.
- Membranoproliferative glomerulonephritis: Approximately 40% of patients with membranoproliferative glomerulonephritis progress to CRF and ESRD in 10 years.
- IgA nephropathy: Approximately 10% of patients with IgA nephropathy progress to CRF and ESRD in 10 years.[1]
- Poststreptococcal glomerulonephritis: Approximately 1-2% of patients with poststreptococcal glomerulonephritis progress to CRF and ESRD. Older children who present with crescentic glomerulonephritis are at greatest risk.
- Lupus nephritis: Overall, approximately 20% of patients with lupus nephritis progress to CRF and ESRD in 10 years; however, patients with certain histologic variants (eg, class IV) may have a more rapid decline.

More on Glomerulonephritis, Chronic

Overview: Glomerulonephritis, Chronic
Differential Diagnoses & Workup: Glomerulonephritis, Chronic
Treatment & Medication: Glomerulonephritis, Chronic
Follow-up: Glomerulonephritis, Chronic

References
Further Reading

Next Page »

Print This Email This